CLINICAL PRACTICE

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Hymenoptera-Sting Hypersensitivity

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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A 24-year-old woman reported that a "bee" stung her upper lip while she was drinking from a can of soda at a picnic. Within 5 minutes, her lips swelled, and she became hoarse and light-headed and had difficulty swallowing. Diffuse flushing and urticaria also developed. She was taken to a local emergency department and received intramuscular epinephrine and intravenous fluids along with H_1-antihistamines. Her symptoms resolved, and after 3 hours of observation she was discharged with an epinephrine auto-injector. How should her case be managed from this point forward?

THE CLINICAL PROBLEM

Although anaphylaxis due to an insect bite has been reported in a small number of cases, stings from insects belonging to the order Hymenoptera are among the most important causes of systemic allergic reactions. The Hymenoptera insects whose stings cause allergy are generally from three families: Apidae (honeybees and bumblebees), Vespidae (hornets, wasps, and yellow jackets), and Formicidae (fire ants) (Table 1 and Fig. 1).

The sting apparatus of hymenoptera is a modified ovipositor (no longer used for egg-laying), and therefore only the female insects can sting. Although the venom from stings can be used to disable and capture prey, most insects sting to defend themselves and their nests. Hymenoptera deliver between 50 ng (fire ants) and 50 μg (bees) of venom with each sting.[2,3] The venoms in hymenoptera contain vasoactive amines, including histamine and dopamine, as well as norepinephrine and kinins, which account for the painful, erythematous swelling and itching at the site of the sting.[4,5] The major allergens leading to systemic reactions in allergic persons are primarily protein enzymes (phospholipase, hyaluronidase, and acid phosphatase).[6] The venom from fire ants contains small amounts of proteins but substantial amounts of toxic alkaloids, which are responsible for the characteristic vesicles (Fig. 2). The molecular characteristics of the venoms from the three families of Hymenoptera are sufficiently different that there is very little antigenic cross-reactivity. Within families (e.g., vespids), there can be substantial cross-reactivity among the allergens present in the venoms; however, honeybee and bumblebee allergies are distinct.[6,7]

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In sensitized persons, a sting can cause the injected venom to bind to venom-specific IgE on mast cells, cross-linking high-affinity IgE receptors and subsequently leading to the rapid release of mast-cell mediators, including histamine, leukotrienes, prostaglandins, and platelet-activating factor. The released mast-cell mediators can cause a spectrum of allergic reactions, from local reactions (affecting small or large [≥10 cm] areas) or urticaria to anaphylaxis and even death. Patients with large local reactions usually do not have a systemic reaction to subsequent stings (with systemic reactions occurring in <10% of these patients), nor do chil-

KEY CLINICAL POINTS

HYPERSENSITIVITY TO HYMENOPTERA STINGS

- Stings from insects of the order Hymenoptera are important causes of systemic allergic reactions.
- In sensitized persons, venom that is injected by a sting binds to venom-specific IgE on mast cells, with the subsequent release of mast-cell mediators that cause allergic reactions ranging from local reactions or urticaria to anaphylaxis and even death.
- Acute systemic allergic reactions typically occur very rapidly after a hymenoptera sting but may be delayed for several hours or be biphasic.
- The treatment of a hymenoptera-induced anaphylactic reaction (as for anaphylaxis caused by any other trigger) is the prompt administration of intramuscular epinephrine.
- Patients who have had a systemic reaction to an insect sting should be referred to an allergist–immunologist for testing for venom-specific IgE.
- Subcutaneous immunotherapy should be considered routinely in patients who have had a systemic allergic reaction to an insect sting and who have a positive test result for venom-specific IgE.

dren with isolated urticaria.[6,7] However, a previous systemic reaction in a patient with venom-specific IgE is associated with a high risk of subsequent systemic reaction, which may occur in 30 to 60% of these patients.[6-11]

Anaphylaxis due to a hymenoptera sting causes at least 40 deaths per year in the United States, although this number is probably an underestimate.[1,6] Severe systemic allergic reactions occur in approximately 0.4 to 0.8% of children and 3.0% of adults.[7,12-15] Although honeybees are more docile than yellow jackets, the honeybee sting is more likely to lead to a systemic allergic reaction. The venom from Africanized honeybees (so-called killer bees) does not differ substantially from that of other honeybees, but Africanized honeybees tend to attack in swarms, and life-threatening or fatal toxic reactions may result when hundreds of these honeybees sting.[6,7] In rare instances, delayed reactions to stings of unknown mechanism can occur, including serum sickness–like reactions, encephalitis, peripheral and cranial neuropathies, glomerulonephritis, myocarditis, and the Guillain–Barré syndrome.[6,7,16]

STRATEGIES AND EVIDENCE

IMMEDIATE MANAGEMENT

The short-term management of hymenoptera stings depends on the clinical manifestations. Treatment of the sting site and local and systemic reactions are addressed below.

Local Reactions

Most hymenoptera stings cause acute pain and transient, localized swelling. These local reactions usually require no treatment other than symptomatic therapy with cold compresses or ice, analgesic agents, oral H_1-antihistamines, or topical glucocorticoid creams or ointments to reduce pruritus and local pain and swelling.[1,6,7] Honeybees (but not bumblebees) often leave their stingers, and these can be removed by scraping the skin with a fingernail or credit card. However, unless the stinger is removed within 20 to 30 seconds, the venom sac is typically emptied.[6,7,17] The intense local inflammation from a sting may cause the appearance of lymphangitic streaks in the first 24 to 48 hours, but this manifestation should not be mistaken for cellulitis.[6,7]

Large local reactions are not usually dangerous, unless they are on the face and compromise the airway, which may occur especially in the case of a sting on the tongue or pharynx. If a local reaction is very large or the associated inflammation results in substantial problems, clinical experience suggests that oral glucocorticoids may be helpful.[1,6,7]

Infections at the site of stings are very rare (especially in the first 2 days), and antibiotic agents are not typically indicated.[1,6,7] In the case of fire ants, sterile pseudopustules (Fig. 2) may occur 1 to 2 days after a sting. The vesicles should be kept clean and left unperturbed to minimize the risk of secondary infection.[1,7]

Table 1. Characteristics of Hymenoptera.*

Common Name	Taxonomic Classification	Size	Nesting Habits	Feeding Habits	Aggressiveness
		mm			
Honeybee	Family Apidae *Apis mellifera*	15–20	Tree cavities and artificial hives	Nectar and pollen	Nonaggressive
Africanized honeybee	Family Apidae *Apis mellifera*	15–20	Natural hives	Nectar and pollen	Aggressive
Bumblebee	Family Apidae Bombus species	12–25	Underground tunnels	Nectar and pollen	Nonaggressive
Fire ant	Family Formicidae *Solenopsis invicta*	4–6	Mounds in disturbed soil	Omnivorous	Aggressive in defense of mounds
Paper wasp	Family Vespidae Polistes species	20–25	Single layer hanging from eaves, porches	Nectar and arthropods	Aggressive in defense of nests
Yellow jacket	Family Vespidae Vespula species	15–20	Multilayered, usually underground	Scavengers	Very aggressive
White-faced or bald-faced hornet	Family Vespidae *Dolichovespula maculata*	25–35	Multilayered, usually in open areas	Nectar and arthropods	Aggressive in defense of nests
European hornet	Family Vespidae *Vespa crabro*	25–35	Multilayered, usually in open areas	Nectar and arthropods	Aggressive in defense of nests

* Adapted from Freeman.[1]

Systemic Reactions

Acute systemic reactions typically occur very rapidly after a hymenoptera sting but may be delayed for several hours or be biphasic. Biphasic reactions occur in less than 20% of episodes and are defined as an initial reaction followed by a recurrence of symptoms (typically in ≤8 hours) after the resolution of the initial episode.[6,7,18-21] The factors associated with an increased risk of severe reaction include being stung by a honeybee (greater risk than with other hymenoptera), underlying mast-cell disorders with elevated serum-tryptase levels at baseline, a previous severe reaction, preexisting cardiovascular disease, and concomitant treatment with a beta-blocker, angiotensin-converting–enzyme (ACE) inhibitor, or both.[1,6,7,21] Beta-blockers potentiate the negative inotropic and chronotropic effects of mast-cell mediators and inhibit the beta-agonist effects of epinephrine used to treat anaphylaxis. ACE inhibitors prevent the breakdown of neuropeptides and bradykinin, which are released as a result of mast-cell degranulation. Anaphylaxis can present with a spectrum of signs and symptoms affecting multiple organ systems, including the skin, gastrointestinal tract, cardiovascular system, nervous system, and both the upper and lower respiratory tracts (Table 2); hallmarks of anaphylaxis are the development of hypotension or the involvement of more than one organ system.[7,21]

Overall, the more rapid the onset of symptoms of anaphylaxis, the more severe the reaction tends to be.[7,21] Death from anaphylaxis typically results from upper-airway obstruction or cardiovascular collapse.

The treatment of hymenoptera-induced anaphylactic reactions is the same as the treatment for anaphylaxis caused by any other triggers and depends on the manifestations of the reaction.[7,21] At the earliest signs of an anaphylactic reaction, either the patient or a companion should administer injectable epinephrine, if available, into the muscle of the mid-anterolateral thigh, and the patient should be transported promptly to an emergency department. The dose of epinephrine is 0.01 mg per kilogram of body weight in a 1:1000 (1 mg per milliliter) solution, with a maximum dose of 0.5 mg in an adult and 0.3 mg in a child. There are no contraindications to the use of epinephrine for the immediate treatment of anaphylaxis, including preexisting cardiovascu-

lar disease, hypertension, or the concomitant use of beta-blockers.[7,21] Delays in administration are associated with more severe reactions and an increased risk of death.[7,21]

The administration of epinephrine should be repeated (at intervals of 5 to 15 minutes) if the patient has persistent or refractory symptoms or a recurrence of symptoms. Most patients require only one or two doses.[7,21] In children, a cutaneous reaction with diffuse urticaria is not indicative of anaphylaxis and, in the absence of other manifestations of anaphylaxis, typically does not require the use of epinephrine. Treatment with H_1-antihistamines is recommended in this context and also as adjunctive therapy in patients treated with intramuscular epinephrine.[6,7]

The treatment of anaphylaxis in the emergency department should include epinephrine for any patient who has more than cutaneous symptoms; epinephrine should also be considered in adults with urticaria alone. H_1-antihistamines can help relieve cutaneous signs and symptoms. For respiratory symptoms, supplemental oxygen and inhaled beta$_2$-agonists should be used. For patients with hypotension, volume resuscitation is indicated, with 1 to 2 liters of 0.9% (isotonic) saline infused rapidly (e.g., a dose of 5 to 10 ml per kilogram in the first 5 to 10 minutes in an adult, and 10 ml per kilogram in a child).[21] Glucocorticoids are often used also, although evidence is lacking to support their effectiveness in patients with hypotension. Patients who have received epinephrine and have a resolution of symptoms should be observed for at least 2 hours for a possible recurrence and, at discharge, should be given instructions about the possibility of a late-phase allergic reaction.

LONG-TERM THERAPY

AVOIDANCE OF EXPOSURE

It is prudent for persons with a history of systemic allergic reaction to avoid areas with a high risk of exposure (e.g., yards, gardens, trash containers, and outdoor areas with uncovered food and drink), to refrain from walking outside barefoot or while wearing sandals, and to wear long sleeves, long pants, a head covering, and gloves when working outside. All patients who have had a systemic reaction to an insect sting and those who have frequent, unavoidable exposure to stinging insects (e.g., beekeepers) should receive a prescription for an epinephrine auto-injector (Auvi-Q, available in doses of 0.15 mg and 0.3 mg, Sanofi; EpiPen, available in a dose of 0.3 mg, and EpiPen Jr, available in a dose of 0.15 mg, Mylan Specialty; or

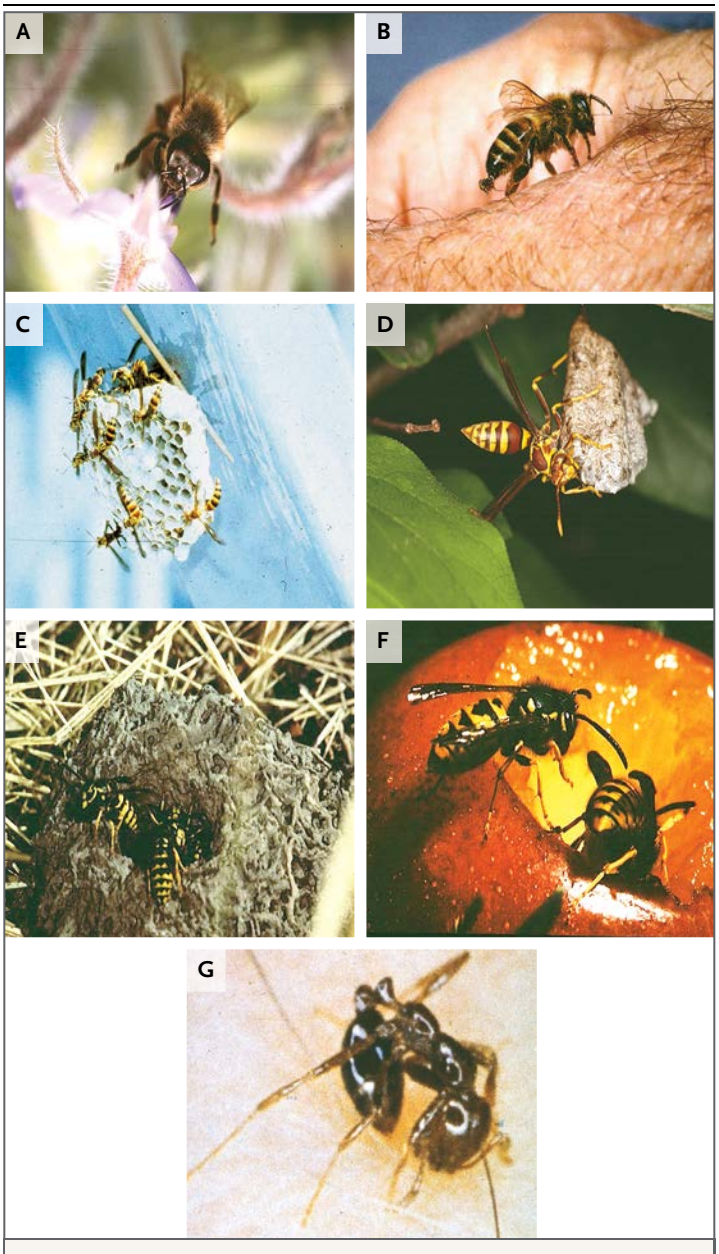

Figure 1. Hymenoptera.
Shown are stinging insects belonging to the three families in the order Hymenoptera — Apidae, Vespidae, and Formicidae. Panel A shows honeybees (family Apidae) gathering nectar, and Panel B a honeybee sting that results in evisceration. Panel C shows a paper-wasp nest (family Vespidae), which is often found under the eaves of a house, and Panel D a close-up view of a paper wasp. Panel E shows a yellow jacket (family Vespidae) in a ground nest, and Panel F a close-up view of a yellow jacket. Panel G shows a fire ant (family Formicidae). Photos courtesy of Dr. Jeffrey Demain.

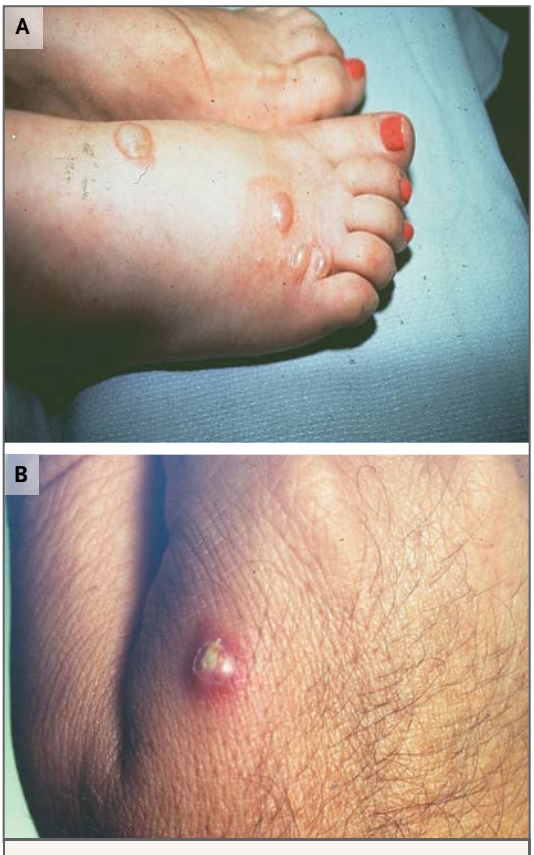

Figure 2. Typically Appearing Pseudopustules Resulting from Fire-Ant Stings.

Panel A shows pseudopustules on the feet of a child, and Panel B pseudopustules on a hand of an adult. Photos courtesy of Dr. Jeffrey Demain.

Adrenaclick, available in doses of 0.3 mg and 0.15 mg, Amedra Pharmaceuticals).

Patients (or, for children, their caregivers) should be instructed to carry an auto-injector with them whenever there is a chance of a sting, and they should be educated regarding how and when to use the auto-injector. In some cases, the treatment for an anaphylactic reaction requires more than one injection[22]; therefore, a prescription for more than one auto-injector should be considered. Patients at relatively low risk for anaphylaxis are those who have a history of only large local reactions to stings or strictly cutaneous systemic reactions, those receiving maintenance venom immunotherapy, and those who have completed more than 5 years of venom immunotherapy.[7] For patients at relatively low risk for anaphylaxis, the decision to obtain an epinephrine auto-injector can be made on an individual basis, after discussions between the physician and the patient.

EVALUATION

Patients who have had a systemic reaction to an insect sting should be referred to an allergist–immunologist for skin testing and possibly in vitro testing for insect-specific IgE,[7] since persons who have a positive test result may benefit from subcutaneous immunotherapy (see below). A large local reaction without a systemic reaction is generally not considered to be an indication for such testing[7] unless exposures are frequent or unavoidable.

The extracts available for skin testing include venom from honeybee, yellow jacket, white-faced hornet (also called bald-faced hornet), yellow hornet, and wasp. For fire ants, venom extract is not available commercially, but whole-body extract is. If patients have a negative response to skin testing but a convincing history of anaphylaxis after an insect sting, in vitro testing for IgE antibodies or repeat skin testing should be considered before immunotherapy is ruled out, especially if the patient's systemic reaction included upper-airway obstruction or hypotension.[23-25]

False negative skin or serum venom-specific IgE testing may occur within the first few weeks after a systemic reaction to an insect sting; patients with a negative early test should be retested 6 weeks later.[26] Waiting 6 weeks for initial testing is not advisable, because some patients may need to initiate venom immunotherapy immediately for safety reasons. It is possible for persons with negative venom skin tests to have systemic reactions to subsequent stings.[23] Some cases of anaphylaxis due to sting may be non–IgE-mediated or may be attributable to subclinical (indolent) mastocytosis.[8,9] Expert guidelines recommend that patients with a severe reaction to an insect sting undergo a workup for mast-cell disorders consisting of a baseline measurement of the serum-tryptase level and, in some instances, a bone marrow biopsy.[7]

In the United States, a sting challenge is not part of the standard management of insect-sting hypersensitivity. Sting challenges can result in systemic reactions,[10,27] and a negative challenge does not preclude a subsequent systemic reaction to stings.[10,28]

IMMUNOTHERAPY

Subcutaneous immunotherapy should be considered in all patients who have had a systemic allergic reaction to an insect sting and who have a positive skin test (Table 3) or a positive result on an in vitro test for venom-specific IgE antibodies.[7] With respect to adults who have had only a cutaneous reaction, there is not a consensus regarding the use of venom immunotherapy, although a joint task force from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology generally recommends this therapy.[7] Children 16 years of age or younger who have had isolated cutaneous systemic reactions to insect stings have a very low risk of subsequent reactions and do not require venom immunotherapy.[29,30]

Venom immunotherapy is also generally not necessary in patients who have had only a large local reaction, because their risk of subsequent systemic reactions is relatively low. However, patients with unavoidable or frequent exposures (e.g., beekeepers) may benefit, because observational data indicate that, after immunotherapy, local reactions are reduced in size and duration.[31,32]

Controlled trials of subcutaneous immunotherapy have shown a significant reduction, to less than 5%, in the risk of a subsequent systemic reaction to an insect sting.[7] In cases in which patients have systemic reactions to subsequent stings despite immunotherapy, these reactions are generally milder than pretreatment reactions.[33] Venom extracts for honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp are available for immunotherapy, as is whole-body extract for fire ants. In the United States, a commonly used extract for therapy is the mixed vespid-venom preparation (100 μg each of venoms from yellow jacket, yellow hornet, and white-faced hornet).

The duration of venom immunotherapy should be at least 3 to 5 years.[34,35] Approximately 80 to 90% of patients who undergo immunotherapy for 3 to 5 years do not have a systemic reaction to a future insect sting.[36-44] Studies have shown that treatment for 5 years is associated with a greater suppression of allergic sensitivity and a lower risk of relapse than treatment for 3 years.[42,45] There are no reliable means of discerning which persons will have a relapse after stopping venom immunotherapy; however, the risk of relapse is higher among patients with a history of severe anaphylaxis with shock or loss of consciousness than among those without such a history. In the patients at higher risk, venom immunotherapy may be continued indefinitely, although the added benefit and cost-effectiveness of indefinite therapy are unclear.

The recommendations for immunotherapy with whole-body extract from fire ants are generally the same as those for immunotherapy with venom extracts.[1] However, data are lacking to guide the duration of fire-ant immunotherapy. Survey data indicate that therapy is commonly continued for 3 to 5 years; some physicians discontinue therapy when results of skin testing or in vitro testing become negative.[46]

Table 2. Clinical Features of Anaphylaxis.

Organ System	Signs and Symptoms
Nervous system	Feeling of doom, weakness, headache, dizziness, and seizure
Eyes, nose, and mouth	Pruritus, angioedema, rhinitis, lacrimation, and metallic taste
Respiratory system	Hoarseness and difficulty swallowing, asthma symptoms, asphyxia, and cyanosis
Cardiovascular system	Tachycardia, arrhythmia, hypotension, myocardial infarction, and cardiac arrest
Gastrointestinal system	Nausea, vomiting, abdominal pain and cramping, and diarrhea
Cutaneous system	Pruritus, flushing, urticaria, and angioedema

Table 3. Criteria for Positive Skin Tests.

Venom or Extract	Result Indicating Presence of Specific IgE Antibodies
Venom from honeybee, yellow jacket, white-faced hornet, yellow hornet, or wasp	Positive intradermal skin test at ≤1.0 μg/ml
Whole-body extract from fire ant	Positive skin-prick test at ≤1:100 wt/vol or positive intradermal skin test at ≤1:1000 wt/vol

AREAS OF UNCERTAINTY

Research is needed to improve the identification of patients at risk for relapse after stopping venom or extract immunotherapy in order to better understand which patients might benefit from ongoing treatment. The current guidelines for

Table 4. Type of Sting Reaction and Recommended Subsequent Management.

Reaction	Recommendation*	
	Children	Older Adolescents and Adults
Large local reaction	Further workup not recommended routinely†	Further workup not recommended routinely†
Cutaneous systemic reaction	Further workup not recommended routinely‡	Diagnostic testing and immunotherapy§
Anaphylaxis	Diagnostic testing and immunotherapy§	Diagnostic testing and immunotherapy§

* The recommendations for children apply to those younger than 16 years of age. For adolescents 16 years of age or older, the recommendations for adults apply.
† The risk of anaphylactic reaction is extremely low among these patients.
‡ Further workup is not recommended routinely because of the low risk of clinically significant allergic reactions.
§ The risk of anaphylaxis is more than 60% in these patients. However, if appropriate immunotherapy is started, the risk of anaphylaxis decreases to less than 5%. If indicated, skin-prick testing and serum-specific IgE testing should be performed to determine appropriate venom allergens. Immunotherapy is indicated for patients with a positive skin-prick test or positive serum-specific IgE testing. Obtaining a baseline serum-tryptase level is recommended for patients who have had a severe anaphylactic reaction.

the testing of allergies to venom are based on a history of systemic reaction, but half the deaths from insect stings occur with a first sting[7]; research is needed to identify patients at risk for such reactions before one has occurred.

GUIDELINES

In 2011, the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma, and Immunology; the American College of Allergy, Asthma, and Immunology; and the Joint Council of Allergy, Asthma, and Immunology published updated guidelines regarding the recommended treatment of hypersensitivity to insect stings.[7] The recommendations in this article are generally consistent with these guidelines (Table 4).

CONCLUSIONS AND RECOMMENDATIONS

In patients with Hymenoptera allergy, such as the patient described in the vignette, venom immunotherapy is the standard of treatment and can prevent life-threatening anaphylactic reactions. Epinephrine is the mainstay of treatment for patients who have a severe reaction to a hymenoptera sting; patients with a history of a systemic allergic reaction should be instructed regarding the need to carry an epinephrine auto-injector and to use it as needed — including possibly more than one injection per reaction.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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